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OF

THE NEW YORK ACADEMY OF MEDICINE

INCORPORATED 1851

AUGUST, 1934

PUBLISHED MONTHLY BY

THE NEW YORK ACADEMY OF MEDICINE

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BULLETIN OF
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GENERAL REVIEW OF OUR PRESENT KNOWLEDGE OF THE VITAMINS*

H. C. Sherman

I.

Some General Principles

Knowledge of the vitamins has now become so extensive, and particularly its different branches have in recent years diverged so widely from each other, that it seems no longer possible to summarize the whole subject in a single lecture in a symmetrical or balanced fashion and at the same time explicitly enough to be of service to those who would put this knowledge to practical use.

For the purpose of the present symposium, therefore, it seems best for me to leave many important matters entirely to the other speakers, and to attempt in this talk merely (1) to emphasize those aspects of the basic science of the subject which now seem sufficiently established to be used confidently in practice, and (2) to speak very briefly on a few selected topics regarding individual vitamins whose

*Delivered November 1, 1933.

significance may be of special interest to the physician—for while I am not trained in medicine, I have been especially requested to address myself this evening, in-so-far as I can, to the point of view of the practitioner. At least we can meet on the ground of a common interest in the enhancement of health.

I shall not begin by defining the vitamins. I do not know any good definition for vitamins as a group; and I think I do know some good reasons for not attempting any.

Firstly, and *most fundamentally,* the fact should be fully realized and constantly kept in mind, that it is only as an accidental result of their having been discovered in a more rapid succession than they could be physically isolated and chemically identified that the vitamins ever came to be grouped together and called by a group name. *They are not a natural group.* The more we learn about them the less alike do they appear, whether in chemical nature or in nutritional function.

Each vitamin is entirely specific in the sense that no one or combination of them can take the place of any other one.

While details of molecular constitution are still being worked out, enough is known of at least vitamins A, B, C, and D to show that these four substances belong to four radically different types of organic compounds.

Correspondingly, their functions in the body are radically unlike.

Whenever, then, the physician has reason to think that he may be dealing with a vitamin deficiency—or, if not with a manifest deficiency, then with a condition in which a more liberal vitamin intake would be beneficial—the question *which* vitamin becomes increasingly insistent as the unlikeness of the individual vitamins is rendered constantly clearer by current research.

And the practitioner's utilization of present scientific knowledge of the vitamins can proceed with the greater confidence in view of the fact that none of the postulated

additions to the present list of vitamins represents any strictly new concept such as might overturn our present views—they all represent rather the refinement of present views through subdivisions of existing concepts.

Thus a few years ago the refinement of knowledge of vitamin B led to its subdivision into two parts: a more heat-labile, now called vitamin B or B_1; and a more heat-stable, now called vitamin G or B_2. Each of these two parts is now apparently in process of being again subdivided, the first into B_1 and Reader's B_4[1]; the second by the setting off of what Chick and Copping call the Y factor from the rest of vitamin G or B_2[2]—in each case a differentiation rather than the introduction of any radically new concept.

Secondly, two independent digests of the knowledge available up to about 1932, each representing a concensus of expert opinion, one British[3] and the other American[4], comprehending the clinical as well as the laboratory point of view, have recently made available a sufficiently well-balanced, well-matured body of subject-matter and interpretation, so that in many respects the physician can now feel that he has as well authenticated a basis for his practical judgments in matters respecting the vitamins as in many older fields.

In the British report, which explicitly states that every part of its text represents the study and judgment of all of its authors, it is stated that: "So far as Western civilization is concerned, it is no doubt true that the rareness of the occurrence of frank deficiency diseases, such as scurvy, xerophthalmia and beri-beri, indicates that an absolute deficiency of vitamins scarcely ever exists in the individual diet. On the other hand, it is now becoming generally recognized that much subnormal health and development, and even incidence of disease, are associated with a partial deficiency of one or more of these necessary substances. The influence of such partial deficiencies, even when relatively slight, may be extremely serious when they occur in early life . . . There is also danger that the effects of such

partial or latent deficiency may persist as a chronic condition throughout adult life." . . . And they emphasize the statement that, *"latent deficiency disease* is a real thing and not an imaginary concept."

In the volume issued by the American Medical Association, Mendel writes: "Existing knowledge permits little more than vague speculation respecting the mode of action of vitamin A . . . For the present it may be wiser to stress the indefinite function of the vitamin in preserving 'health and vigor' rather than to herald any specific action against definite microbiotic enemies. Deficiencies of any sort tend to decrease the ability of the body to resist disease." And in another article of the series, Eusterman and Wilbur, writing explicitly from the clinical standpoint say: "Until recently the versatility of vitamin A has apparently not been appreciated." Thus the fact that vitamin A is entirely specific among the vitamins in the sense that no other can take its place, is consistent with the fact that its function in serving the well-being of the body and as an *aid* to the ability to resist infection may be a more "versatile" or more generalized function than that of aiding against a single species of pathogen.

Hess, writing on vitamin C in the same series of articles says: "Another point that has been brought into prominence in connection with adult as well as infantile scurvy is its intimate association with the infectious process . . . one of the most striking and important symptoms of scurvy is a susceptibility to infection (furunculosis, nasal diphtheria, grippe, etc.)."

Thus while each vitamin is a specifically essential substance for which no other known substance can be substituted, yet shortages of certain vitamins may increase the body's susceptibility to more than one species of infection —yet, again, this does not mean to *all* infections equally.

A third general principle to be borne in mind is that, whatever therapeutic properties individual vitamins may possess, *a vitamin is primarily a nutritional factor.*

Thus in the introduction to a recent concise review contributed by the Department of Physiological Chemistry at Yale[6] we read:

"The mass of pertinent experimental evidence at present available forces the conclusion that the conception of the vitamins is not a fad; indeed, it is rapidly ceasing to be looked upon even as a biochemical novelty but is rather accepted as one of the fundamental principles of nutrition."

Perhaps it should be emphasized, even at the risk of repetition—that the practitioner will often realize most satisfaction from thinking of the vitamins as nutrients rather than as drugs.

The British Committee's remark of some years ago upon the blurring of the nutritional significance by "pharmacological bias" still holds food for thought. Any practitioner may at any time be dealing with cases in which no vitamin can supply the specific pharmacodynamic action that is desired, yet in which whatever medication is employed will yield a more satisfactory result if attention is also given to the general nutritional well-being of the body by ensuring a liberal intake of any vitamin of which there may conceivably have been even a relative shortage. Thus, in the clinical article already referred to, Eusterman and Wilbur, after referring to the rarity of xerophthalmia in the United States, add: "It is likely, however, that certain individuals, the poor in particular, do not consume enough foods that contain vitamin A and vitamin G to insure a state of nutrition essential to the greatest physical stamina, efficiency, and ability to resist infectious diseases." And Wilder, in his address as Chairman of the Section on Pharmacology and Therapeutics at the Eighty-second Annual Session of the American Medical Association, referred to "the increasingly probable condition of mild or incipient avitaminosis" and further said: "I am convinced that many cases of dissatisfaction with treatment are accounted for by the partial starvation which results from incompletely balanced diets . . . In many

diseases the possibilities of therapeutic benefit from supplying nutritional elements in amounts greater than those required for maintenance in health is today receiving augmented attention."

Then too, the physician, in addition to employing the newer knowledge of nutrition not to supplant but rather to supplement his accustomed therapeutic methods, has also the opportunity to teach the patient (while *as patient* he or she is in a teachable frame of mind) how to acquire and maintain throughout the rest of life a nutritional condition superior to that which he would otherwise enjoy—or endure. The degree of well-being which is prevalent in the community need by no means be accepted as representing the physician's objective for his patient. No less high and conservative an authority than F. Gowland Hopkins has stated[5] that, "a race or community is found in equilibrium with an environment which includes its food supply. It is often forgotten that such environment is fortuitous and that the equilibrium reached is one in which the community, while managing to survive, may yet be functioning at levels far below those possible to its innate capacities. It is truths of this sort that the science of nutrition, having reached the stage of controlled experiment, is now demonstrating." He also says:

"It is often felt that concerning matters so urgent as our own nutrition, humanity, with all the experience of the ages behind it, can have little to learn from modern science, yet, as in the case of so many other established traditions, an assumption of this kind is wholly unjustified. Tradition accumulates prejudices quite as often as truths, and the former are apt to be more potent in their influence." . . . And:

"That scientific research during recent years has greatly emphasized the importance of right nutrition as a factor in human welfare is very sure . . . We now know that conditions recognized as actual diseases develop because the supply of some minute nutritional necessity has failed, while, short of obvious disease, ill-health may depend upon

a lesser degree of such deficiency . . . In all individuals such a lack may greatly increase the liability to infection by bacteria and other parasites."

So much for the general consideration of the topic assigned me. The following brief statements regarding individual vitamins are all intended to be construed in the light of these general principles: (1) the highly specific nature of each vitamin in the sense that nothing else can take its place; (2) the possibility that a vitamin may nevertheless have a bearing upon the ability of the body to resist more than one species of infection; and (3) the general principle that a vitamin is primarily a nutritional rather than a pharmacological factor—and may, on that account, be all the more important to the physician who takes the long view of the well-being of the patient.

II.

Some Observations with Reference to Individual Vitamins

Vitamin A is a fat-soluble substance conspicuously essential to growth, and also very important to the maintenance of vigorous health at all ages.

In addition to the effect of vitamin A in maintaining, as the Journal of the American Medical Association puts it, the integrity of the body's first line of defence against infection, it also has a further influence. For in the carefully controlled experiments both of Lassen in Copenhagen and of Boynton and Bradford in Rochester, it was found that when infective organisms were introduced by injection so that the battle was staged entirely beyond the 'first line of defence', the ability of the body to resist the infection was again found much higher in the animals which had received the more liberal intakes of vitamin A. This is not necessarily a matter of the immunological mechanism as now understood; but it is a fact which we are probably not justified in ignoring, even if we cannot yet fully understand it.

Time does not permit more than the mention here of the very large amount of laboratory evidence that vitamin A taken in amounts above those which actual necessity requires, yields increasingly beneficial results in higher levels of vitality or standards of positive health.

Hess, Lewis, and Barenberg, in the Journal of the American Medical Association for August 26, 1933 discuss the question, "Does Our Dietary Require Vitamin A Supplement?" I think the answer should depend upon the dietary. Their controlled observations in a model child-caring home have not indicated decrease of respiratory infections as a result of increasing the intake of vitamin A above that which the dietary of the institution regularly afforded.

The 24 ounces of milk mentioned as regularly contained in their daily dietary probably by itself furnished each of these children well over 1500 International units of vitamin A per day; other articles of their liberal dietary enrich it still further in this respect; and these children probably entered the periods of controlled observation with fairly good stores of vitamin A already laid up in their bodies. A large proportion of the children of the United States and of New York City are less fortunate in these respects. May we therefore hope that the careful observations of Hess, Lewis and Barenberg will be interpreted to the credit of the nutritional condition of the children under their care, and not to the discredit of vitamin A?

Their findings constitute strong evidence against the exaggerated impressions which they and some others in this country and Harris and some others in England believe to be more or less prevalent; but perhaps it should be pointed out that where in such researches the evidence is conflicting, that which represents positive findings is usually fully as significant as that which is negative.

There is positive ("field") evidence of wide differences of vitamin A intake even among people of like economic status, depending upon their food habits, and there is also positive (laboratory) evidence that the dietaries richer in vitamin A tend to yield better results in the long run; but to avoid any possible misconception may I emphasize in the same sentence that I am speaking of such enrichment of vitamin A intake as may be had by the wise use of everyday articles of food?

Vitamin B (B_1). This is the substance the study of which as a preventive of beri-beri called general attention to the vitamin concept about 20 to 25 years ago. It was found that the neuritis of beri-beri could be prevented (and if not too far advanced could be cured) by many natural foods, and that from these foods a specific antineuritic substance could be extracted. The existence of this substance was established and the investigation of it was well advanced, before the coining of any such word as vitamin.

The outstanding characteristics of vitamin B are its antineuritic value and its value for the maintenance and promotion of appetite.

Its properties as a growth-essential and as in some way helping to keep the body in good tone and resistant to some types of infection, may be equally important but are less distinctive since some of the other vitamins also serve in such ways as these.

Speculations as to just "how it acts in the body" have perhaps been even more rife around vitamin B than about the other vitamins. Few if any of the other theories rest upon such substantial experimental evidence as does Cowgill's view[4,6], that while "the question of the exact function of this vitamin remains unsolved" there is a quantitative relation between the vitamin B requirement and the total energy metabolism or requirement. This point of view, with a full realization of the important influence

of vitamin B upon the appetite, may often be of therapeutic value. Varying circumstances may well lead to different answers in different cases as to when one should employ a vitamin B concentrate and when enrich the intake of vitamin B by increasing the proportion of the natural or less highly refined articles of food in the diet. The former will, of course, suggest itself in those cases in which a very large or very sudden increase is desired, while the latter has the advantage that it contributes to the enrichment of the intake of other important nutritional factors at the same time.

In the presence of Dr. Hess who has investigated so extensively both vitamins C and D and of Dr. Mendel whom we always wish to hear as often and as fully as opportunity permits, I shall but mention these two vitamins and then close with a few observations regarding vitamin G or B_2.

Vitamin C prevents and cures scurvy; but if we were sure that we should never see a case of scurvy we would still have ample reason to be interested in vitamin C. Hess has described how often children without distinctive scurvy symptoms are yet in need of more vitamin C in order to do their best. Wolbach, Howe and Church have shown the importance of vitamin C to the nutrition of the bones as well as of the soft tissues; and discussion in a recent issue of the Journal of the American Medical Association suggests that more liberal intake of vitamin C may perhaps be helpful in combating arthritis. Dolldorf relates it to capillary condition. Very likely our knowledge of the ways in which vitamin C serves the nutritional welfare of the body is still far from complete; yet already enough is known to suggest strongly that diets rich in vitamin C may be helpful in a wide variety of cases even if not specifically indicated by the symptoms observed.

Vitamin D is perhaps as dramatically effective against rickets as is vitamin C against scurvy. Is it, then, also a nutritional asset in which it is desirable to enrich the diet liberally at all ages? There are others present who can discuss this question better, so I leave it to them.

Vitamin G has so recently been differentiated from vitamin B that on many points much yet remains to be done to assess the relative responsibilities and merits of these two essential substances. It might be premature to assign to vitamin G any such clear-cut pharmacological function as that of vitamin B in the prevention and cure of beri-beri; but the suggested relationships of vitamin G both to pellagra and to pernicious anemia, and its recently demonstrated relation to the development of cataract all seem to call for careful consideration of the possibility that diets rich in vitamins A, C, and G may be helpful in a number of connections. We know that vitamin G has far-reaching effects on the well-being of our experimental animals.

Supplementing the summaries already mentioned ([3,4,6]) reference may also be made to the still more recent summary paper of Day[7].

As Day points out, Goldberger and Lillie[8] were the first to describe the pathological condition in the rat due to a deficiency of what is now termed vitamin B_2 or G. Other laboratories soon confirmed and extended their general findings[9,10,11,12,13].

Goldberger and associates produced also an experimental condition known as black-tongue in dogs, and from similarities of symptoms (and their observations to the effect that all could be prevented or cured by the feeding of the same materials) they were led to suggest[14] that pellagra in man, black-tongue in dogs, and the condition chiefly characterized by dermatitis in rats are all due to the same nutritional deficiency. In commenting upon this theory Underhill wrote[4]: "The discovery of the potency of the unknown factor termed vitamin G is an undoubted advance in the knowledge of pellagra, but it is clearly unwise to assume that vitamin G deficiency and pellagra are necessarily synonymous terms."

The caution thus suggested by Underhill would seem to be doubly justified, on the one hand by the developments in

the study of pellagra, and on the other by the fact that vitamin G deficiency is now known to give rise to other important effects in addition to the pellagra-like dermatitis.

Particularly important are the eye conditions described by Day and his coworkers[7,15] and independently confirmed by O'Brien[16] and by Yudkin[17].

Thus vitamin G deficiency may be both less and more than clinical pellagra. Here as elsewhere, the attempt to assign the vitamin a physiologically or pharmacologically descriptive name is apt to throw undue emphasis upon what (however important in itself) is only one feature of its nutritional significance.

The work of Ellis in the writer's laboratory[18] is affording strong evidence that a higher level of intake of vitamin G may distinctly influence the degree of nutritional well-being and resulting health and vitality, even though the lower intake is already above that at which any characteristic sign of nutritional deficiency appears.

We therefore believe that vitamin G not only prevents deficiency disease but has positive functions in normal nutrition as well, and that optimal nutrition requires a much more liberal intake of vitamin G than simply that which is demonstrably necessary for the prevention of any characteristic sign of deficiency.

In the foregoing discussion the term vitamin B or B_1 is allowed to stand for the whole of the more heat-labile, and the term vitamin B_2 or G for the whole of the more heat-stable, part of the vitamin B complex. The writer has no doubt that each of these two primary divisions of the vitamin-B complex is a multiple rather than a simple nutritional factor; but the necessity for brevity forbids the attempt to analyze the evidence in this paper. The nutritional considerations here briefly summarized will lose nothing of their significance when it becomes possible to assign them, or if necessary to reassign them, as properties of more precisely defined chemical substances.

As I began by saying that we have no definition of the vitamins, I may end by saying that we do not know how many vitamins there are. We have, however, good ground for believing that our present concepts cover the essentials and that further discoveries will be differentiations within the lines already well conceived; and will therefore not upset or supplant our present knowledge of the vitamins but rather supplement and refine it.

There is much knowledge now at hand which seems certainly sound so far as it goes; and I believe that it goes far enough to be capable of rendering good service to medicine, not only in remote contingencies but also in everyday practice.

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THE EFFECTS OF MODERATE DEFICIENCY OF VITAMINS*

S. W. Clausen
University of Rochester

The physician in his practice has learned to recognize and to treat successfully the diseases due to the outspoken deficiency of vitamins. Those of us who live in the North know rickets; those in the Orient know beriberi; those in the South know pellagra; a few of the fortunate have seen xerophthalmia; and all are familiar with scurvy. We are told, however, that much ill-health is due to a moderate deficiency of vitamins; that the food of modern mankind, in the process of manufacture, selection and preparation, has lost some of its virtue. The laboratory worker, with his colonies of animals, discovers some half dozen new deficiencies a year; and suggests that symptoms in man, similar to those of his animals, are due to similar deficiencies. The manufacturer, given a little time, is able to furnish a preparation containing the indicated vitamin —succeeds in having clinical trials made, and finally so advertises the product to physician and often to layman, that the physician does not dare to neglect prescribing it for vague symptoms which puzzle him. Considerable money changes hands—some not infrequently finding its way into the research laboratory which holds the patent. But I would like to remind you that the real evaluation of each and every one of these remedies rests with the clinician. The physician Eijkman, in Java, noted that pigeons fed for economical reasons on boiled polished rice from the hospital kitchens, developed polyneuritis, resembling that of patients with beriberi. The Danish pediatrician, Bloch, showed that xerophthalmia and night blindness could be cured by cod liver oil, but not by sunlight; also that these conditions occurred independently of rickets;

* Delivered, November 1, 1933.

thus clearly proving that the disease is not akin to rickets, and furnishing evidence of the existence in cod liver oil of two vitamins. The clinical experiments of Dr. Alfred Hess have established the value of vitamin C in the prevention and cure of infantile scurvy; and have greatly clarified the problem of the nature and action of vitamin D in rickets. I would further remind you that a coöperation is proper and necessary between the reputable manufacturer and the clinician in the study of the wider, more vague, field of moderate vitamin deficiencies.

The physician who undertakes to prove that any morbid condition is due to a lack of a specific vitamin, must establish four criteria: (1) The condition in question must disappear wholly or in part when the vitamin is administered. This, however, may not occur, if irreparable damage has been done; if the vitamin is not absorbed, as may happen, with fat-soluble vitamins in steatorrhea; and if other deficiencies are not corrected. For example, diets deficient in vitamin D are often also deficient in calcium and phosphorus. Very often also, a morbid condition may be due to several factors. The development of infectious diseases depends upon exposure; virulence of the infecting organism; resistance of the host. Diet in such cases cannot be expected to afford complete protection; only a careful statistical analysis can afford any proof of the existence of a significant deficiency of a vitamin. (2) Administration of the vitamin must prevent wholly or in part the development of the morbid condition. (3) The beneficial effect, if any, ascribed to the vitamin must be proved not to be due to some other action of the preparation—certain preparations of vitamin B contain sugars, whose caloric value cannot be ignored in producing a gain in weight. Highly purified vitamins—for example A, C and D; possibly B_1—are now available for use in crucial experiments. This question is not merely academic. The proof of a definite deficiency will make possible the proper selection of a dietary of natural foodstuffs. It will counteract the recent tendency to administer to babies mixtures which resemble the fast disappearing shot-gun prescription. (4)

The existence of mild or latent deficiency may be studied by the use of refined methods of measurement. Tests of visual acuity might reveal latent deficiency of vitamin A; the test for capillary fragility of Göthlin may be a measure of deficiency of vitamin C; the X-ray may reveal unsuspected evidence of rickets. Such tests must be interpreted with all due caution. When a research worker discovers by X-ray a form of rickets which does not yield to appropriate treatment, the burden of proving that the condition is rickets still rests with him.

Certain forms of evidence are presumptive; in themselves insufficient, but highly suggestive. The non-existence in his environment of frank cases of beriberi, pellagra, rickets, scurvy or night blindness, is taken as evidence against the existence in the patient of a corresponding latent deficiency. Due regard must then be paid to the special conditions prevailing in the patient—such as illness, early age, rapid growth, pregnancy, which might create an increased need for vitamins. Requirements of an animal species for vitamins cannot be applied uncritically to man, but often have been. The increase of intake of a vitamin far beyond the usual quantity may not relieve a condition, such as the tendency to repeated infection. This cannot be used as an argument that the condition in question may not be aggravated if the intake of vitamin is lowered. Chemical analyses of tissues for vitamins are at present beginning to supplement biological tests. These analyses must be accepted with the greatest reserve; and cannot obviate the necessity for actual clinical trial of a carefully planned diet. They may be of great value in conjunction with delicate tests for the actual presence of disease due to the deficiency.

We may now turn to a consideration of some of the more definite evidence of latent dietary deficiency. In spite of the marked decline in death-rate from diarrhea and certain specific contagious diseases, the mortality in the first days of life and the high incidence of prematurity and of still-birth continue. Evidence that faulty diet during

pregnancy may be in large part responsible for this mortality is accumulating. Toverud, working is Oslo, has found that the Norwegian diet especially in winter, results in a negative balance of calcium and of phosphorus; that this can easily be prevented by the use of more milk, green vegetables, fruit, and cod liver oil. The birth-weight of full-term infants was thereby increased; and the percentage of premature births among unmarried mothers dropped from 32 per cent (in the obstetrical clinic) to 2 per cent among the mothers cared for by Toverud. At the Maternity Center of New York by careful supervision of hygiene during pregnancy, the incidence of premature births has been reduced to 1/3 of that prevailing in the general population of the City. Several factors of course play a role in the decrease of the rate of premature birth. The dietary deficiency undoubtedly includes that of calcium, phosphorus and vitamin D.

The typical disease due to lack of vitamin D is rickets. Other factors may play an etiologic role—such as the diet of the mother during pregnancy; low birth weight; and rapid growth. The effect ascribed by E. Mellanby to cereals in the production of rickets may in part be due to rapid growth or to the low assimilation of the phosphorus in cereal. The phosphorus of cereals is present chiefly as inositol hexaphosphate; which is not only poorly absorbed but which also precipitates calcium, and thus prevents its absorption. In certain cases of rickets, the typical symptoms and signs, although present, may not be so prominent as signs usually regarded as minor: for example, extreme irritability. We have observed several cases in which the irritability disappeared within a few days, while the serum phosphate rose in response to ultraviolet radiation. In another case, sweating was profuse; the hands were red and swollen, and the skin of the fingers was macerated and infected—suggesting acrodynia. However, the blood pressure was normal and signs of rickets were obvious; the abnormal condition of the hands rapidly disappeared under antirachitic treatment. Such cases may have given rise to the idea that ultraviolet therapy is bene-

ficial in acrodynia. We have not found it so. Another condition allied to rickets, but with none of the skeletal changes is the tetany occurring in children of low birth weight within the first six weeks of life. Such cases usually respond in a dramatic manner to intensive antirachitic therapy. Dental caries in older children has been ascribed by M. Mellanby to dietary deficiency, particularly to a relative deficiency of vitamin D and to a diet high in cereals. Boyd and his coworkers report that dental caries may be arrested by a diet containing pigmented vegetables, fresh fruit, butter, milk and cod liver oil. Hanke and his coworkers believe that the addition of one pint of orange juice and the juice of one lemon to the ordinary diet will check the development of caries. Disagreement prevails among competent workers in regard to the relative effect of diet and of acid-producing microorganisms in causing caries. More carefully controlled clinical studies are now in progress in several places; and we should soon know more definitely which are the important factors.

Definite indications exist that a relative deficiency of vitamin C may exist in certain parts of the world, even where scurvy is rare. Göthlin and his colleagues have refined a test for capillary fragility—first proposed by Dr. Hess; by aid of this, it has been possible to show in two adults that the capillaries of the skin become more fragile after a diet low in vitamin C had been taken for several weeks; and returned to normal within a few weeks after a diet high in vitamin C had been resumed. A rather extensive survey among school children in northern Sweden revealed the presence of a considerable number in whom the capillary fragility was increased. A good correlation existed between this and the low antiscorbutic value of their diets. Gingivitis appeared more frequently in the children with increased fragility, but was present also in the others. Gerstenberger has used fresh fruit in large quantities in the treatment of aphthous and ulcerative stomatitis, apparently with success. Hanke and his coworkers have made extensive studies in which one pint per day of orange juice

appears to have greatly decreased the incidence and severity of gingivitis in a community of children at Mooseheart. They imply that the effect is due to vitamin C. It must, however, be pointed out that owing to its carotene content, orange juice may have a vitamin A activity greater than that of milk. It also contains an appreciable amount of calcium. The anemia in scurvy may yield to orange juice. Rohmer and Bindschedeler describe prescorbutic anemia in infancy—accompanied by poor growth in weight and stature, irritability, anorexia, and puffiness of the face, feet and hands. In several of their cases, cure of the anemia could not be accomplished with a dried cabbage juice rich in vitamin C, until iron also was added.

Deficiency of the vitamin B complex has long been suspected in the dietary of infants, largely on the basis of assays using experimental animals. Maurer, reasoning on rather a priori grounds, believes that neonatal death is due to insufficient vitamin B in the diet of the mothers during pregnancy. The importance of this subject would justify a most extensive study. Hoobler, Bloxsom, Dennett and others have described a symptom-complex in children 6-12 months of age, which they ascribe to relative deficiency of vitamin B. The symptoms are anorexia, pallor, loss of weight or stationary weight, irritability, and muscular rigidity. The symptoms yield to the use of yeast, yeast extracts, and preparations of wheat germ. The effect, however, may be due in large measure to a greater intake of food. From our own experience, we can say that many cases with similar symptoms do not respond to this treatment. We have felt that the chief etiological factors in our cases were faulty methods of feeding, or the presence of infection. In the latter type, we have often observed immediate and lasting improvement following the use of 1 or 2 units of insulin twice a day continued for a week or ten days. Vitamin B may be relatively deficient in the diet of older children. In an admirably planned clinical experiment, Summerfeldt of Toronto, shows that the expected average gain in weight in a group of children can be

increased four times over a period of three weeks by the use of a special cereal, in place of ordinary cereal. These gains were maintained. It is difficult to know whether such gains are really optimal; whether they may reasonably be attributed to vitamin B is also open to some question, because the cereal furnished also considerable additional minerals, including calcium, phosphorus and iron. Patients with chronic diarrhea may be given diets low in vitamins; they may also absorb vitamins poorly. It seems likely that the smoothness of the tongue noted in some of these conditions may be caused by partial lack of vitamin B_2; for it is relieved by giving brewer's yeast.

Vitamin A has been the subject of recent clinical study by Dr. Hess and his colleagues. There can be no doubt from their investigations that the administration of large quantities of vitamin A in the form of haliver oil, or provitamin in the form of carotene, did not confer the slightest additional power upon infants to resist respiratory infections. This is to be attributed to the fact that these children were already receiving a diet rich in vitamin A. According to Sutliff and Segool, cod liver oil will not prevent otitis media as a complication of scarlet fever. We have found that carotene is also ineffective (Figure 1). On the other hand, it seems possible from a study of the carotinoid content of the blood, which we have carried out, that about 15 per cent of children over the age of two years, may avoid foods rich in carotene, and as a consequence about 1/3 of them may be subject to repeated respiratory infection. We feel also that a diet rich in vitamin A may be desirable in the first few months of life. It is known that infants—especially of low birth weight—may have in their tissues a comparatively very low store of this vitamin. Although they may not at this time be subject to infection, owing to the presence of protective substances acquired from the mother, they may later on show increased susceptibility, unless they receive more vitamin A than is present in milk alone. We have carefully studied two groups of infants in the out-patient department.

The Effect of Oral Administration of Carotene During Scarlet Fever

Cases Uncomplicated at Onset			Cases Complicated at Onset			
No Carotene 21 Cases	Carotene 13 Cases		No Carotene —13 Cases—		Carotene —16 Cases—	
		Complications	Initial	After 1 wk.	Initial	After 1 wk.
1	0	Otitis	8	1	8	8
2 (same case)	0	Mastoiditis	0	5	1	13
1	2	Adenitis	2	4	3	2
0	1	Arthritis	0	1	0	0
0	0	Sinusitis	2	0	3	1
0	0	Abscess	1	0	2	3
0	0	Empyema	1	0	0	0
0	0	Peritonitis	0	2	0	0
2	3	Other	0	2	0	2
0	0	Died	—	1	—	1
4.3	5.2	Av. Stay, Wks.	6.9		6.1	

Fig. 1.

Infections of Infants as Affected by Diet

From Barenberg and Lewis, New York City and Maxwell, Rochester, N. Y.

	New York City		Rochester, N. Y.	
	C. L. O.	Viosterol	Good	Bad
J. F. M.	0.35	0.25	0.24	0.50
A. M. J.	.23	.18	.15	.22
J. A. S.	.19	.15	.08	.14
O. N. D.	.33	.17	.23	.32

Fig. 2.

Eighty of these received cod liver oil at least from the age of two months; most of them from the age of two weeks; and until at least the age of six months. From this time, they received pigmented vegetables. The rate of infection (number of infections per infant per month) is nearly the same as that in the series of Barenberg and Lewis (Figure 2). The other group of 40 infants received no cod liver oil; until after the age of four months. Many of them received vegetables from the age of six months. The milder

respiratory infections—rhinitis, pharyngitis, otitis media —occurred with equal frequency in both groups, excepting in the early Spring months (Figure 3). In the various

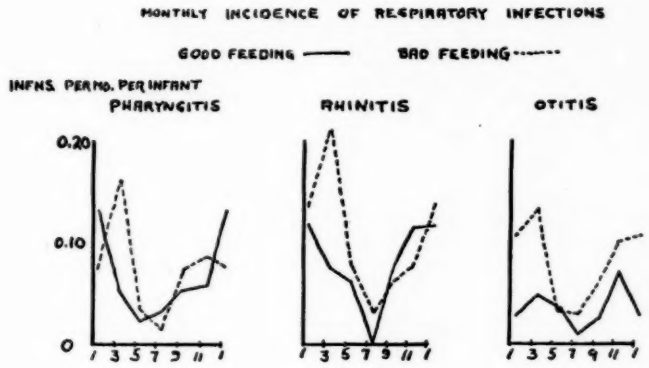

Fig. 3.

age groups, there is little difference in the incidence of rhinitis and pharyngitis, but a marked increase in the incidence of otitis media in the poorly-fed group after the age of six months (Figure 4). We feel that our groups are too small to permit very certain conclusions, and we would emphasize the difficulty in excluding other causes than

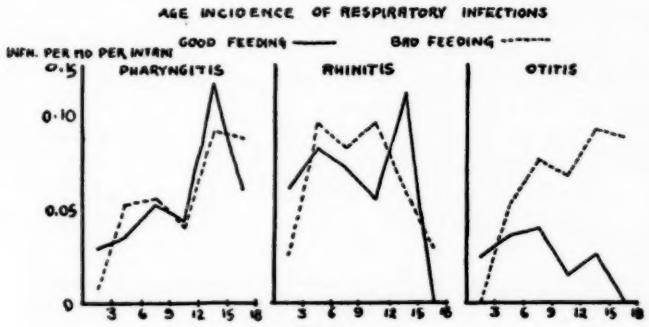

Fig. 4.

faulty diet. In another study, we have some evidence that early feeding of cod liver oil may prevent the occurrence for severe infections, such as pneumonia, mastoiditis, and septicemia (Figure 5). Here we are dealing with only a

Correlation of Infections with Previous Feeding

DIET			0-6 Mos. INFECTIONS, %				6-24 Mos. INFECTIONS, %				
C. L. O.	Veg.	Number	O	Mod.	Sev.	Sev. Total	Number	O	Mod.	Sev.	Sev/Total
0	0	35	40	37	23	0.38	50	14	40	16	0.54
+	0	27	56	29	15	0.34	21	9.5	86	4.5	0.05
0	+						77	25	60	15	0.21
+	+						56	41.1	55.4	3.5	0.06

DIET			2-6 Yrs. INFECTIONS, %				6-14 Yrs. INFECTIONS, %				
C. L. O.	Veg.	Number	O	Mod.	Sev.	Sev. Total	Number	O	Mod.	Sev.	Sev/Total
0	+	267	32.5	55.1	12.4	0.18	712	55.9	39.6	4.48	0.10
+	+	124	60.5	34.7	4.8	0.12	123	62.6	32.5	4.88	0.13

Fig. 5.

single observation in each case, and relying upon the history as well as we could obtain it. In another study we have analysed the records of about 700 children who entered the hospital before the age of three years. We have considered separately the sexes; have indicated the ratio of severe to non-severe infections; and have attempted to correlate the influence of (a) bad diet as causing severity of infection; and (b) exposure to children of school age in the family as causing severity of infection. These two latter correlations are based upon Yule's method of coefficients of contingency. A coefficient of plus one is regarded as a perfect correlation; plus 0.5 as very good; zero, as absence of relation. Good diet is defined as before—cod liver oil from the age of two months to at least six months; either cod liver oil or vegetables from the age of six months. The age-incidence (Figure 6) of relatively severe

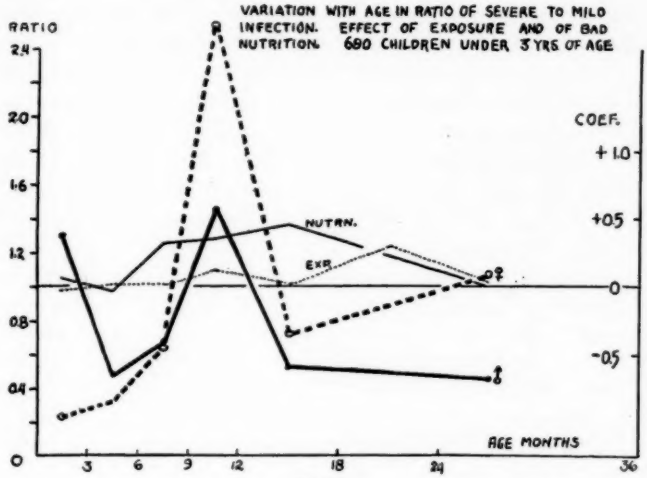
VARIATION WITH AGE IN RATIO OF SEVERE TO MILD INFECTION. EFFECT OF EXPOSURE AND OF BAD NUTRITION. 680 CHILDREN UNDER 3 YRS OF AGE
RATIO
COEF.
+1.0
+0.5
0
-0.5
NUTRN.
EXP.
AGE MONTHS
2.4
2.0
1.6
1.2
0.8
0.4
0
3
6
9
12
18
24
36

Fig. 6.

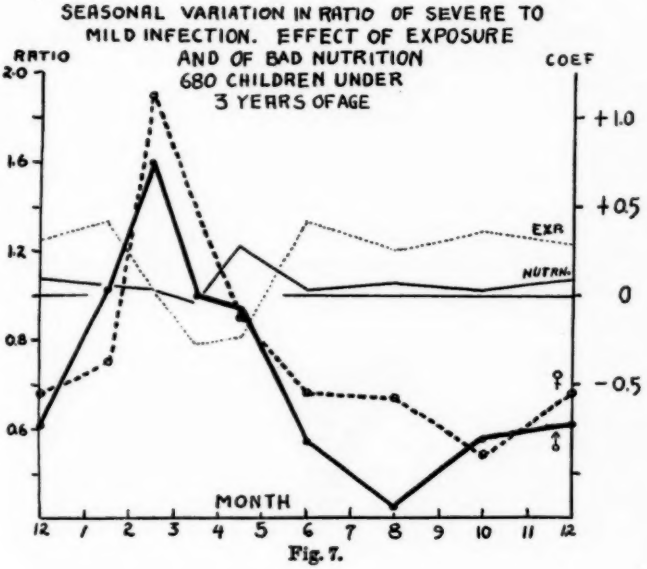
SEASONAL VARIATION IN RATIO OF SEVERE TO MILD INFECTION. EFFECT OF EXPOSURE AND OF BAD NUTRITION 680 CHILDREN UNDER 3 YEARS OF AGE
RATIO
COEF
+1.0
+0.5
0
-0.5
EXP.
NUTRN.
MONTH
2.0
1.6
1.2
0.8
0.6
12
1
2
3
4
5
6
7
8
9
10
11
12

Fig. 7.

infection indicates that boys are relatively much more liable than girls under the age of three months. Thereafter, girls are more liable. This is regarded as an effect of constitution. Exposure to older children—and incidentally—greater economic distress—cannot account for the high incidence in both sexes of relatively severe infection between the ages of nine and twelve months. On the other hand, there is some evidence that the relative severity of infection may be associated with poor diet consumed in the earlier months of life. In the seasonal incidence of severe infections (Figure 7), we observe that the sexes are affected nearly alike; the girls suffering somewhat more at all times. Infants who have a severe infection during the summer months are likely to have had previously a poor diet. The very marked increase in severity of infection in February is not related to exposure, and only to a slight degree related to faulty diet in the earlier months. We may regard this high peak of severe infections as due either to more massive exposure, or to increased virulence of the infection. These studies are not offered with a view of settling the question of the relationship of vitamin A to infection; but rather, in order to keep the question open. They indicate, moreover, that the factors involved in infection are many, including constitution (sex, even during infancy), exposure, the nature of the infection, and probably also diet. I would stress in particular that if vitamin A has any anti-infective power, it should be administered in the earliest months when the growing organism may need larger quantities, and when a deficiency is more likely to exist.

NON-DIABETIC KETOSIS IN CHILDREN*

OSCAR M. SCHLOSS

When katabolism of fat is normal, it is completely burned to carbon dioxide and water and only traces of ketone substances which arise as intermediary products of its oxidation can be detected in the body fluids or in the urine and expired air. The survival of ketone substances due to incomplete fat katabolism leads to their accumulation and excretion in abnormal amounts and gives rise to the metabolic perversion termed ketosis.

It occurs in its severest form as a complication of diabetes and the illuminating investigations in connection with this disease have contributed largely to our knowledge of its mechanism. The occurrence of ketosis of serious magnitude is not, however, confined to diabetic persons. In the young especially, non-diabetic ketosis is not infrequent and may threaten life and require energetic treatment for its alleviation.

It has long been known that young persons affected by various disorders are prone to excrete ketone substances in their urine; but after puberty this tendency is minimized. In adult life, non-diabetic ketonuria of pronounced grade is rarely observed except in starvation and even then, is of much lesser magnitude than is observed in children.

The tendency to ketosis in the young is not confined to the human as shown by Allen's experiments on dogs. A diet high in fat led to very severe ketosis when fed to puppies, but was practically without effect on grown dogs. The tendency of the young to ketosis is obviously an expression of some metabolic peculiarity.

It is my purpose to discuss the non-diabetic type of ketosis as it affects children with special reference to its clinical manifestations; also with such consideration of its etiology and mechanism as our present knowledge of the subject permits.

* Delivered November 2, 1933.

Subsequent to the demonstration by Hirshfield in 1895 that ketosis results from insufficient metabolism of glucose, much has been done to elucidate this action. The observations of Knoop, Magnus-Levy, Schwartz, Embden, and others show that the oxidation of the straight chain fatty acids with an even number of carbon atoms leads to the occurrence of aceto-acetic acid which is oxidized only as a result of the simultaneous combustion of glucose indicating the occurrence of a reaction in which glucose and aceto-acetic acid are involved. The nature of this reaction and all of the forces participating are still undetermined despite many pertinent investigations. Shaffer, however, has shown by in vitro experiments, that in an alkaline medium and in the presence of peroxides, aceto-acetic acid is destroyed by glucose. If aceto-acetic acid is not destroyed, it accumulates in the body fluids being changed in part to beta-hydroxybutyric acid by reduction and to acetone by decomposition. All three substances are excreted in the urine and acetone also in the expired air. Further advances contributed by Zeller, Lusk, Ladd and Palmer, Shaffer, Woodyatt and others have served to clarify the quantitative relationship involved in the ketolytic action of glucose. With certain exceptions, to be mentioned later, it seems that the complete oxidation of aceto-acetic acid requires the simultaneous combustion of definite proportions of glucose. According to this conception, Woodyatt and Shaffer have appraised the ketogenic and anti-ketogenic components of foods metabolized expressing this relationship by means of ratios.

Calculated according to the method of Woodyatt, when the metabolized fatty-acid-glucose ratio exceeds 1.5 in adults, acetone substances appear in the urine. This corresponds to a ketogenic : anti-ketogenic ratio of 1 when computed on a molecular basis by the method of Shaffer. Such ratios must necessarily apply only to material actually metabolized for, aside from the possibility of food escaping absorption, it has been shown by Richardson and Ladd and others that when the diet is high in fat, excess fat may be stored and energy derived from the consumption

of body glycogen. The ratios cited apply only at the threshold of ketosis, for as larger amounts of fat in relation to glucose are metabolized, the actual amount of ketone substances eliminated are much less than these ratios would lead one to expect. Under these conditions, Shaffer found that it was necessary to assume a molecular ratio of 2, twice the threshold value, in order to obtain an agreement between calculated ketone formation and actual excretion. Assuming that the present conception of the destruction of aceto-acetic acid is correct, it appears that the ketolytic action of glucose is somewhat variable. There are, indeed, observations which suggest that there may be modifying influences on this reaction, and it is certain that appraised on the basis of present knowledge, the destruction of aceto-acetic acid in the course of fat katabolism does not constantly and necessarily conform to a strictly molecular reaction with glucose. A very good example of this inconsistency is the smaller ketolytic action of glucose in children than in adults.

The readiness with which children excrete acetone substances in their urine has naturally incited curiosity and investigation. The most illuminating observation in this connection was made by Wilson, Levine and Rivkin. When children metabolize a mixture with a fatty acid to glucose ratio of .7, acetone appears in the urine thus disclosing that at the threshold of ketosis children require twice as much glucose to metabolize completely a given amount of fatty acid as adults. It seems therefore unnecessary to assume that children store or mobilize glycogen less efficiently than adults. Indeed, all experimental evidence is to the contrary. The fact that during fasting the blood sugar declines more rapidly and to a lower level in children than in adults observed by Shaw and Moriarty, Weymuller and Schloss, and others, is easily explained by the greater demand on stored glycogen. It appears therefore that when energy is being supplied largely by the combustion of fat, due usually to restricted carbohydrate ingestion, children need more glycogen than adults thus justifying the assumption that the deficiency in glycogen storage is relative and not absolute.

Accessory influences which favor the ready development of ketosis in children are the normally high metabolic rate which is increased by fever and the diminished carbohydrate intake during fever due to loss of appetite or vomiting. We do not know on what the normally low fatty acid to glucose ratio of children depends, but there is probably, as Allen suggests, some specific biologic factor. This may perhaps be related to the accelerated endocrine growth stimulus during this period. Hints as to the possible influence of the pituitary can be gleaned from the experiments of Anselmino and Hoffman, Houssay and Burns and Ling, but such implications are at present too speculative to merit more than passing notice here.

The mild degree of ketosis so readily developed by all children during the course of acute infections or conditions accompanied by some degree of carbohydrate starvation has, as a rule, no clinical significance, since as far as can be determined, in its milder forms it is not responsible for characteristic symptoms. It seems that these milder forms of ketosis are so controlled that the organism is able to defend itself against harmful effects. In contrast to the usual benign form, there are certain peculiarly susceptible children who develop a degree of non-diabetic ketosis which may prove as severe and threatening as diabetic coma. There is no simple laboratory test or physical characteristic which differentiates children with this susceptibility. They are so designated only by the observation that severe ketosis is provoked by conditions with only trivial effect on other children. The familiar clinical manifestations of ketosis vary in severity from slight drowsiness to severe coma or convulsions. The symptoms are largely referable to the central nervous system and in the milder forms drowsiness or somnolence may be the only objective sign which in most cases disappears even without treatment. Occasionally, however, beginning with slight drowsiness the sensorium becomes progressively duller until the deeply comatose child with flushed face, red lips, air hunger, tissue dehydration, acetone breath, and severe pros-

tration presents a picture which on superficial examination cannot be differentiated from that of diabetic coma. Serious symptoms such as these are not always of gradual onset but may supervene suddenly within the course of a few hours. It seems probable that the tendency to develop severe ketosis is an expression of a constitutional peculiarity of the individual, a magnification perhaps of the susceptibility of children in general, but at any rate, a metabolic fault which renders him liable to severe ketosis provoked by conditions which are without effect on the ordinary person. The existence of this susceptibility is recognized by most observers and is exemplified by observations of Weymuller and myself that when fed diets high in fat, susceptible children develop a grade of ketosis much greater than normal children.

The cause of this peculiar reaction has been the subject of much speculation but its nature still remains obscure. We can, of course, be sure that the fundamental difficulty lies in a disproportion between the relative amounts of glucose and fat metabolized, for even if there were no experimental or chemical evidence for this view the striking effect of glucose administered to children suffering from severe ketosis would be ample proof. But it is when we attempt to elucidate the manner in which metabolism is thus disturbed that difficulty is encountered. In the presence of pronounced ketosis, the blood sugar falls very rapidly and this was considered by Hilliger, Ross and Josephs, Rumpf and others to demonstrate deficient storage of glycogen. Wilson, Levine, and Rivkin, Weymuller, I, and others have observed, however, that under the influence of high fat diets or fasting, the blood sugar of normal children is reduced as much as that of children especially predisposed to ketosis. Moreover, the same observers found no indication that susceptible children stored glycogen less well than normals. Therefore, despite the simplicity and attractiveness of this theory, one must conclude that it is unsupported by sufficient evidence.

Another possibility to be mentioned is that susceptible children may require more glucose for the complete metabolism of fat than normal children, just as normal children use glucose less economically than adults. Unfortunately, there is insufficient evidence to appraise this possibility. To do this, it would be necessary to determine the amounts of glucose and fat actually metabolized by means of the respiratory quotient. So far as I am aware this has been done only once. In a child susceptible to severe ketosis provoked by cyclic vomiting Wilson, Levine, and Rivkin found that the ketogenic-antiketogenic ratio at the threshold of ketosis did not differ from that of normal children. The hypothesis has also been advanced that there may be some inherent difference between children in their tendency to burn fat. The normal child always burns glucose in preference to fat. If the diet is high in fat, excess fat is stored and the composition of the metabolic mixture stabilized by the consumption of stored glycogen. Wilson, Levine, and Rivkin observed that this tendency to restrict the combustion of ingested fat was lacking in a child susceptible to severe ketosis. Weymuller and I noted that when fed identical high fat diets susceptible children developed a much greater degree of ketosis than normal children. We ventured to suggest the possibility that susceptible children have a greater tendency to burn fat than normal and are thus deprived of a useful protective mechanism. Much more evidence is necessary to establish the validity of this hypothesis, but at present it seems of sufficient importance to merit passing mention. On purely speculative grounds one could suggest other perversions of metabolism which might conceivably predispose to severe ketosis, but a consideration of these would offer little illumination of a subject concerning which experimental data is the prime necessity, and for this reason I shall proceed to more practical aspects of the subject about which, fortunately, more is known.

In the clinical laboratory, ketosis is usually recognized by the presence of a positive nitro-prusside test in the urine.

This is a very delicate test and the reaction is striking in the presence of even very small amounts of acetone. As an uncoordinated observation, it designates in no way that ketosis is of clinical importance. Due to disregard of this knowledge, symptoms may be attributed to ketosis which are actually dependent upon another cause, often an obscure infection. A similar misconception is the prevalent belief, chiefly among the laity, that acidosis, a term used erroneously as a synonym for ketosis, is a frequent cause of recurring digestive or febrile disorders. The symptoms of ketosis are clouding of the sensorium, ranging from drowsiness to deep coma, rarely convulsions, prostration, air hunger, dehydration, occasionally vomiting, and so far as we know, this is all.

Ketosis may impair the acid-base balance of the organism leading to acidosis but this does not necessarily occur. The effect of small degrees of ketosis may be so fully compensated that there is no impairment of the functional efficiency of the acid-base balance of the body fluids. Involved in this protective mechanism is the formation of the organic base ammonia leading to the conservation of fixed base, the elimination of carbon dioxide by the lungs, and the excretion of acid in the urine. When the degree of ketosis is too great to be compensated, the acid-base pattern of the blood becomes distorted by the utilization of base to neutralize ketone acids. The magnitude of this distortion is in direct proportion to the quantity of ketone acids present at that time. In addition, however, ketone acids are excreted in part at least in combination with fixed base and if ketosis is severe or prolonged, the total fixed base of the body may become depleted. The loss of fixed base as shown by Gamble and his collaborators leads also to loss of water and dehydration may thereby be induced. The presence and degree of acidosis can be best measured in the clinical laboratory by determination of the carbon dioxide content or capacity and the reaction of the blood or serum. For clinical use, knowledge of the carbon dioxide content or capacity of the blood, although not infallible, is usually sufficient.

Thus far I have emphasized the tendency of the ketone acids to cause acidosis but strict accuracy demands brief mention of the exceptional association of ketosis with alkalosis. Haldane and his collaborators observed that the alkalosis of overbreathing or anoxemia may be accompanied by the excretion of ketone substances in the urine. Of more practical importance is the influence of loss of hydrochloric acid by vomiting. If a chlorine deficit be thus induced the blood bicarbonate may be increased even in the presence of considerable ketone acid. Alkalosis of this origin is disclosed by analysis of the blood for chlorine and bicarbonate.

Since the emphasis by Stadelman and subsequent observers of acidosis as the cause of the symptoms of diabetic coma, it has generally been assumed that the symptoms of ketosis are of this origin. The usual association of acidosis with severe ketosis and the observation that acidosis induced in experimental animals by injection of mineral acids causes symptoms quite comparable to those observed in human ketosis suggests strongly that acidosis plays an important part in the causation of symptoms. Moreover, in the non-diabetic ketosis of children there is usually a close correlation between the degree of ketonemia, the presence and degree of acidosis, and the presence and degree of symptoms.

Despite this evidence, the possibility that symptoms may be due to direct toxic action of the ketone substances must be considered. It is known that the administration of acetone to experimental animals may cause profound coma. Hurtley and Trevan found that neutral derivatives of acetone and aceto-acetic acid caused in animals symptoms not unlike those of diabetic coma even including pronounced air hunger. Owing to the neutrality of the substances used in their experiments, they assumed that acidosis was not produced, but they record no data which show that it was not present. All of the evidence bearing on this problem is indirect and is based on the toxic action of ketone substances when given to animals. Until more

evidence is available, the possibility that the ketone substances may cause symptoms directly through their toxic properties must be considered.

Probably the simplest and most easily understood cause of ketosis is the restricted carbohydrate intake of starvation. Under such circumstances, available stores of glycogen are quickly consumed, fat is burned to supply energy and the aceto-acetic acid arising from its combustion finds insufficient glucose to complete its destruction. Except when used for therapeutic purposes, starvation in children results from refusal of food or vomiting. Rarely, however, and then only in the extremely susceptible child does the ketosis of simple starvation cause serious symptoms. Ketosis usually is pronounced after 24 to 48 hours, but despite continued starvation it gradually becomes less intense and may disappear entirely. The blood sugar of fasting children falls very quickly but begins to increase within a few days and may reach normal figures. The alleviation of ketosis by starvation is probably due in part to lowering of metabolism, the restricted consumption of fat, and the utilization of glucose from tissue protein. Whether as an additional protective mechanism, fat is converted into glucose is at present a question too uncertain and controversial to discuss here.

If starvation accompanies a febrile infection, a greater degree of ketosis usually occurs. The accelerated metabolism of fever leads to early depletion of glycogen stores and increased fat consumption. Under these conditions, many of the severe cases of ketosis occur. The type of infection apparently plays no specific role for the same child may develop severe ketosis with successive infections of different types. Scarlet fever, pneumonia, tonsillitis, measles, and other infections may act similarly on the susceptible child.

Starvation preceding and following surgical operations, especially in the presence of a febrile post-operative reaction, is a frequent cause of severe ketosis but with the possible added influence of the anesthetic, so far as has

been determined, involves no other mechanism than has been discussed.

It is probably in relation to so-called recurrent or cyclic vomiting that non-diabetic ketosis in children has aroused most interest. The term has been used to describe a syndrome in children characterized solely by repeated episodes of incessant vomiting always provoked by ingestion of food and water, often spontaneous, lasting in severe cases for as long as a week. After a period of progressive weakness and emaciation, vomiting ceases and recovery ensues. Fatalities rarely occur. The nature of so-called recurrent vomiting is obscure and it is probable that there are different precipitating causes. One child may have an attack at the onset of any acute infection and another may have typical episodes without apparent cause. Sedgwick and Taylor called attention to the importance of chronic infections of the tonsil, a relationship proved by the effect of tonsillectomy in a group of cases sufficiently large to be convincing. This is in accord with my own experience.

Bad posture and visceroptosis were thought by Talbot and Brown and others to predispose to recurrent vomiting.

In many cases, the affected children are of a neurotic type with a neuropathic background and the attacks may be precipitated by any emotional crisis. It therefore seems unlikely that the ultimate cause of so-called recurrent vomiting is single and constant.

With the discovery by Marfan that the urine of such patients contains acetone and perhaps diacetic acid, the belief that ketosis is of etiological importance has become prevalent, indeed to such degree that the term acetonemic vomiting is often used as a synonym especially in the French and German literature.

It is evident that starvation resulting from such severe vomiting will cause ketosis, the degree of which will vary in different individuals and in children especially susceptible, ketosis may be of such magnitude to cause symptoms. This is entirely in accord with all of our conceptions

but ketosis as the primary event directly responsible for the vomiting is an entirely different conception which requires some analysis. Vomiting is a recognized but inconstant symptom of ketosis. Although it may occur during the ketosis of starvation or high fat diets, it does not occur with regularity and when it does occur it is not as persistent or as severe as in recurrent vomiting. Indeed, vomiting may be entirely absent even when ketosis is as severe as that which may accompany an attack of recurrent vomiting. With the exception of a few experiments, attacks of typical recurrent vomiting have not been induced by the ketosis of starvation or high fat diets even in children known to be susceptible to such attacks. The theory that ketosis is the primary event rests largely on the observations of Marfan, Edsall and a few others that acetone may be detected in the urine before the onset of vomiting but it must be pointed out that such observations are few and that frequently acetone is absent from the urine even after vomiting has commenced.

It seems impossible, therefore, that ketosis is of constant etiological importance in so-called recurrent vomiting. That there may be a small group of cases in which such relationship exists is of course possible, but even this assumption would require further and more convincing evidence. It is quite in accord with present knowledge that recurrent vomiting is usually accompanied by ketosis which may be severe but is to be regarded merely in the same light as ketosis which occurs under other conditions.

Obviously, the most important therapeutic measure for the treatment of ketosis, regardless of its cause, is the administration of glucose. When retained it can be given by mouth, if not, it may be given by rectum or by subcutaneous, intraperitoneal or intravenous injection. Glucose even in isotonic solution causes some degree of peritoneal irritation and is absorbed slowly from subcutaneous tissue; therefore, when its need is at all urgent, intravenous injection is the most desirable method of administration. Either a 6 or 10 per cent solution may be used dissolved in freshly distilled water or half normal saline. If the 10

per cent solution is used, 20 c.c. per kilogram of body weight is adequate for the first injection and this is repeated in 3 to 6 hours depending on the symptoms. The injection of this amount should require at least one hour, preferably two, in order to avoid diuresis and resulting dehydration. The intensity of treatment must be gaged by the degree to which the symptoms are relieved. Of chief value for this purpose are hyperpnea, the degree of drowsiness, the intensity of the acetone odor of the breath, and of most value, the carbon dioxide content of the blood. The acetone in the expired air may be estimated roughly by the degree of turbidity produced in the Scott-Wilson reagent. Of least value is the qualitative test for acetone in the urine. Small changes in the excretion of ketone substances are not thus disclosed and acetone may be present in the urine for some time after acute symptoms have disappeared. A rapid decrease of the intensity of the nitro-prusside test, however, is a valuable indication that ketosis is subsiding. The ferric chloride test for acetoacetic acid is much less sensitive and for this reason gives information of more value.

Before the nature and mechanism of ketosis were understood the resulting acidosis was emphasized and was treated by the administration of large amounts of alkali. This practice is no longer current but to some degree the idea that sodium bicarbonate must be given still persists. For this reason, the rationale of its use is worth considering. When glucose is given in adequate amounts the ketone substances are destroyed and disappear from the blood. The base bound by the ketone acids is thus liberated and the normal acid-base pattern of the blood is restored. It is certain that alkali is unnecessary to neutralize the ketone acids in the blood. Ketosis can be cured quickly and completely without the use of bicarbonate.

In long continued or very severe ketosis, however, the excretion of the ketone acids may deplete the body to some degree of fixed base and to compensate for this loss small amounts of sodium bicarbonate, Darrow's solution or the sodium lactate solution of Hartmann and Senn may be

given, but it is well to emphasize that this treatment is accessory and not essential.

Associated with the loss of fixed base, there is loss of body water with resulting dehydration which, if extensive, may require treatment. If sufficient water cannot be ingested and if the amount given with glucose is inadequate, salt solution must be given by subcutaneous injection. The administration of sodium chloride in this fashion has the additional advantage of replenishing the electrolytes of body fluids.

Some have recommended the use of insulin in addition to glucose with the idea that the glucose would thereby be rendered more effective. Certainly in the ordinary case of ketosis, the use of insulin is not indicated on theoretical grounds for there is no evidence of pancreatic insufficiency. The blood sugar is below normal and the urine does not contain sugar.* It is possible, however, that it may accelerate the combustion and thereby the ketolytic action of glucose and in this way induce more speedy recovery, but the existence of this action and its efficacy as a therapeutic measure can only be demonstrated by further experience.

In this necessarily brief account, I have touched upon current opinion concerning the mechanism of ketosis and have dwelt somewhat upon the non-diabetic form as it affects children. It is unnecessary for me to recount the many deficiencies in our present knowledge of ketosis, both from the viewpoint of physiology and of the clinic. Unfortunately, perhaps, I have emphasized them too freely. In the course of time, however, many of these deficiencies will be supplied and it seems best, in the meanwhile, to reckon consciously with their existence rather than to attempt to fill the gaps insecurely and temporarily with unwarranted speculation.

* Very rarely one encounters severe ketosis in non-diabetic children accompanied by high blood sugar and glycosuria. The subsequent history of the patient reveals no diabetic tendency. The exact nature of such ketosis is unknown but it seems possible that it is dependent upon temporary pancreatic disturbance. At any rate, it would seem that insulin is clearly indicated in the treatment of cases of this type.

CHARLES DARWIN (1758-1778) AND THE HISTORY OF THE EARLY USE OF DIGITALIS*

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I. *Introduction.*

Before me lie two books, one a great classic in the history of medicine, the other a little known graduating dissertation of an Edinburgh medical student. William Withering's *An account of the foxglove and some of its medical uses* was published in Birmingham in 1785. It is a document that would satisfy the medical humanist, as well as the most rigorous scientific thinker, for its prose compares favorably with the best of the 18th century; and its clinical descriptions of the action of digitalis are clear, shrewd and incisive. His deductions, moreover, are based upon a painstaking analysis of evidence, all in the highest tradition of modern scientific medicine.

The medical thesis, on the other hand, which is entitled *Experiments establishing a criterion between mucaginous and purulent matter. And an account of the retrograde motions of the absorbent vessels of animal bodies in some diseases,* was published in the town of Lichfield in 1780, five years before Withering's book, and two years after its lamented author had died of a dissection wound. In this thesis one also finds an excellent description of the therapeutic action of foxglove. The author of this remarkable booklet bore the name of Charles Darwin, and one is astonished to discover that he died in the year 1778, before having attained the twentieth year of his age. The name of Charles Darwin is sufficient in itself to arouse curiosity, and for some five years I have been attempting to collect

* An abstract of a paper read January 10, 1934, at the meeting of the Section of Historical and Cultural Medicine, New York Academy of Medicine. The full text with illustrations, contemporary letters and bibliography will be published separately as a brief monograph.

information concerning his career, and concerning the early history of the use of digitalis. My paper, however, which has resulted from this enquiry, will have more to do with Darwin than with digitalis.

The hereditary transmission of mental traits and capacities is nowhere more strikingly illustrated than by the Darwins, who for five successive generations have produced men of outstanding attainments. I need, therefore, scarcely apologize for describing the career of an early and little known member of this remarkable family. Charles Darwin of this memoir died at the age of 19 years and 7 months, a youth of precocious achievements, full of promise and intellectual vigor. His abilities were of a most unusual character; indeed he made so great an impression upon men of his time that, even after 150 years, it has not been difficult to trace from contemporary sources many details of his brief career.

II. *Early Education.*

Charles Darwin was the eldest son of Erasmus Darwin (1731-1802), physician, naturalist, and poet, by his first wife, Mary Howard, the daughter of Charles Howard, a merchant of Lichfield in Shropshire. Charles was born September 3, 1758, in Lichfield when his mother was but 18 years of age. A second son, Erasmus Jr., was born in 1759 and died tragically, probably by his own hand, in 1799 at the age of 40. Erasmus Jr. was given to writing poetry and he had become a successful, though rather eccentric, solicitor in Lichfield some years before his death. Two other children of Mary Howard by Erasmus Darwin died in infancy and the third son, Robert Waring Darwin, who was born in 1766, became a Fellow of the Royal Society at the age of 22 for a paper on ocular spectra (*Philosophical Transactions*, 1788, vol. 76), and was the father of Charles Robert Darwin, naturalist and author of the *Origin of species*. Mary Howard, the mother of these three able boys, became the victim of an obscure disease, probably nephritis incident to child-bearing, and died in 1770, thirteen years after her marriage, when she was scarcely 30 years of age.

Many have commented on the striking fact that Erasmus Darwin transmitted his characteristic qualities of mind to his descendants, and from a close study of Erasmus, the father, and of his son Charles, it seems to me that these peculiar qualities were perhaps more strikingly present in Charles than in the other children. The available data is not complete, but what exists is highly significant. In the short memoir of Charles written by his father as an appendix to his thesis, it is stated that from his infancy he was "accustomed to examine all natural objects with more attention than is usual: first by his senses simply; then by tools, which were his playthings—By this early use of his hands, he gained accurate ideas of many of the qualities of bodies; and was thence afterwards enabled to acquire the knowledge of mechanics with ease and with accuracy; and the invention and improvement of machines was one of the first efforts of his ingenuity, and one of the first sources of his amusement.

"He had frequent opportunities in his early years of observing the various fossile productions in their native beds; and descended the mines of *Derbyshire,* and of some other counties, with uncommon pleasure and observation. He collected with care the products of these countries; and examined them by such experiments, as he had been taught, or had discovered: hence he obtained not only distinct but indelible ideas of the properties of bodies, at the very time when he learnt the names of them; and thus the complicate science of chemistry became not only easy, but delightful to him."

It seems that Charles had inherited stammering from his father and it was the hope that he might be cured by learning French early in life. He was therefore sent to Paris with a private tutor, the Reverend Mr. Dickenson, rector of Blimhill in Shropshire, who was said to have been modest, learned and scientific. During the two years Charles spent with him in Paris no conversation was allowed in English, and Charles returned completely cured of his stammering.

In discussing his son's education, Erasmus gives free expression of his opinion of contemporary pedagogical methods in the following remarkable passage:

"Ye classic schools! ye not only overcome the struggling efforts of genius and bind his Proteus-forms, till he speaks the language you require; but you then divert his attention from the nice comparison of things with each other, and from associating the ideas of causes and their effects; and amuse him with the looser analogies, the vain verbal allusions which constitute the ornaments of poetry and of oratory! . . . Mr. *Darwin* acquired a competent knowledge of the latin and greek languages, chiefly by reading books of useful knowledge, or which contained the elements of science: and which were more agreeable to him than the monstrous and immoral tales of heathen mythology, or of fabulous history. He was of opinion, that to study these dead languages so accurately as to criticise their beauties, and at a time when all their books of real value had been repeatedly translated, was a prodigality of labour, which might suit the retirement of a pedant, but was unbecoming an active philosopher: that to acquire a taste for greek poetry by years of ill-employed industry, was not much more important than to acquire the power of playing well on some one musical instrument: and that, in the schools of language as in the schools of drawing a man of science would learn the use of the pen and pencil, as far as they are concerned in the expression or communication of distinct or useful ideas; but to waste the first twenty years of life in learning the metaphors of language, or the drapery of drawing might serve those, who made poetry or painting a profession; but was liable to disqualify the mind of the more energetic pursuits of business or philosophy."

Erasmus Darwin saw in Charles the following traits which he attributed to his mother's influence and inheritance:

"Nor amid these acquirements of knowledge was his taste for morality neglected; for his ingenious mother, even to her latest hour! instilled into his breast a sympathy with the pains and with the pleasures of others, by sympathizing herself with their distress or exultation; she flattered him into a sense of honour by commending his integrity, and scorn of falshood [sic], before her friends: and taught him prudence by pointing out to him the ill consequences of the bad conduct of others, whose names or persons he was acquainted with: and as she had wisely sown no seeds of superstition in his mind, there was nothing to overshade the virtues, she had implanted."

Charles presumably stayed at the Lichfield school until early in 1775. At all events there is no further record of him until he matriculated at Christ Church in Oxford, and

there the only existing record concerning him is the matriculation entry. It reads as follows:

> "Charles D.
> S. Erasmus of Lichfield W. Staff.
> Ch. Ch. Matriculated 30 March 1775 age 16."
> (Foster's *Alumni Oxoniensis*).

Charles spent nearly a year at Christ Church, but he came to dislike the atmosphere intensely feeling that his mind was going to seed in the pursuit of "classical elegance," and he "sigh'd to be removed to the robuster exercises of the medical schools of Edinburgh."

III. *Edinburgh.*

Charles Darwin went to Edinburgh late in 1775, or early in 1776 and, apart from occasional trips home, he remained there until his death. From a letter to him from his father dated April 2, 1776, one gains the impression that by that date he was well established in the University.

The school of medicine at Edinburgh in the second half of the 18th century was the most vigorous in Europe. Robert Whytt, the professor of the institutes of medicine (physiology) [1747-1766], had a few years earlier discovered the principle of reflex action (1751). The experimental method was also being inculcated in students by his successor, William Cullen [1766-73] and by *his* successor, James Gregory, who was professor of the institutes from 1776 until 1781. Alexander Monro, II, the anatomist, also gave strength and versatility to the school, and added much to the stimulating intellectual atmosphere of the great community in which they lived. It was the Edinburgh of this period that created Benjamin Rush, and others of that virile group which established the medical school of the University of Pennsylvania shortly before the Revolution.

Charles Darwin had the good fortune to become intimate with Andrew Duncan, a rising clinical teacher of the Edinburgh school (professor of the theory of medicine, 1790-1819). Duncan took Charles to live in his house and gave

him personal guidance during his early years and access to the wards of the Royal Infirmary soon after he had entered the school. During these years Charles apparently kept in close touch with his father, and letters still in existence give an intimate first-hand picture of the things about which they corresponded, and incidentally of the things that were stirring the imagination of this observant and enthusiastic young student, namely new ideas and modes of therapy then in use.

In the brief interval between the autumn of 1775 and the time of Charles Darwin's death, May 15, 1778, he completed his medical studies and won the esteem of all his teachers. For the Aesculapian Society at Edinburgh he submitted, in competition for their annual gold medal, a dissertation on the differences between mucus and pus. For this essay, Darwin received in March 1778 the gold medal offered by the society. For his graduating dissertation he chose as a subject the lymphatics and prepared a conventional thesis in classical Latin. This was translated by his father and republished in the volume mentioned above under the title *An account of the retrograde motion from the absorbent vessels of animal bodies in some diseases.* This was a more remarkable piece of work than the dissertation on pus and mucus, and it reflects the current teachings of Edinburgh concerning the relations of the lymphatics to dropsical conditions, and it also illustrates a very considerable independence of mind and a capacity to obtain evidence from well-conceived experiments.

A note on page 126 of Charles Darwin's dissertation states "There are other ingenious works of the late Mr. Darwin in the Hands of the Editor, which may perhaps at some distant Time be given to the public, if the medical World seems to require them." This note naturally aroused curiosity and to a certain extent it has been satisfied through the discovery in the Medical Society of London of an unpublished manuscript of 67 pages by Charles Darwin entitled *What are the established varieties of the pulse, their causes & uses in medicine.* Since studies on the pulse are mentioned in Erasmus's letters to Charles, April 1776,

it is likely that the dissertation on the pulse represents one of his earliest pieces. This document reveals his powers as an observer more clearly than the two published dissertations mentioned above, and it illustrates, incidentally, that he had an excellent grasp of relevant contemporary literature on the heart and circulation. He discusses the causes and significance of the variations in the pulse and gives a clear description of normal variation with age and of the effect of various physiological states such as exercise, rest, eating, somnolence, etc.

No other unpublished manuscripts by Charles Darwin have been found.

Little wonder that the untimely death of such a youth should cause profound regret that found expression in a most surprising variety of channels. The circumstances of his death are described in the following paragraph from an anonymous obituary published in *Medical and Philosophical Commentaries* (Edinburgh, 1778, *5*, 329-336).

"About the end of April, Mr. Darwin had employed the greatest part of a day in accurately dissecting the brain of a child which had died of hydrocephalus, and which he had attended during its life. That very evening he was seized with severe head-ach. This, however, did not prevent him from being present in the Medical Society, where he mentioned to Dr. Duncan the dissection he had made, and promised the next day to furnish him with an account of all the circumstances in writing. But the next day, to his head-ach there supervened other febrile symptoms. And, in a short time, from the hemorrhagies, petechial eruption, and foetid loose stools which occurred, his disease manifested a very putrescent tendency. And, notwithstanding the skill of Drs. Cullen and Black, who attended him from the beginning of his affection; notwithstanding the anxious care and attention of his father, Dr. Darwin, a physician of great eminence in England, who arrived at Edinburgh some days before his death, his disease at length terminated fatally."

In addition to three detailed obituaries published within a few weeks of his death, accounts of Darwin found their way into contemporary biographical dictionaries such as Hutchinson's *Biographia medica,* and later into the *Biographie universelle* (vol. 10). Much the most interesting contemporary document, however, is an anonymous poem entitled *An elegy on the much-lamented death of a most ingenious young gentleman, who lately died in the College*

at Edinburgh where he was a student. Only one copy of this has been traced and it was sold in 1931 by Messrs. Blackwell of Oxford to Mr. Paul B. Victorius, then of New York and now of London, who has generously allowed me to have the title-page reproduced and a rotograph made of the text. A manuscript note attributes the elegy to 'Mr. Jackson,' though not identified with certainty, it is possibly Richard Jackson, a prebendary, who was living in Lichfield in 1778, or John Jackson, the historian of Lichfield. There are references throughout the elegy to Charles's early education, his reading of learned authors, his interest in observation of natural objects and to his instincts for collecting.

Dr. Andrew Duncan's affection for Charles Darwin was such that he caused him to be buried in his family vault in the Chapel of Ease of St. Cuthbert's at Edinburgh, now known as the Buccleuch Parish Church Burying Ground. The tablet is the first one on the South wall of this vault and it bears among other things the inscription "He cultivated with success the friendship of ingenious men and was buried by the favor of Dr. A. Duncan in this his family vault."

Such then was the career of the first Charles Darwin, and it would almost seem that Nature, thwarted in her first endeavor, caused another Charles Darwin to see the light of day.

IV. *The Darwins and digitalis.*

One of the remarkable features of Charles Darwin's book is a description of the therapeutic effects of the decoction of foxglove. Nine case histories are given, appended rather casually on pages 103-112 after the following heading: "A note belonging to *page* 65, *and* 68." One would naturally infer that they were cases seen and described by Charles himself, for there is nothing, except their position in the text, to suggest that they were inserted by his father. They are prefaced by the following sentence: "The foxglove has been given to dropsical patients in this country with considerable success: the following cases are related

with design to ascertain the particular kinds of dropsy, in which this drug is preferable to squill, or other evacuants." The case-reports are important since they contain the first accurate description of the therapeutic effect of digitalis in cardiac oedema published in any language, antedating Withering's celebrated book, *An account of the foxglove,* by five years.

The question arises whether these cases were described by Charles or by Erasmus. There is no direct statement in the book, but the evidence is overwhelmingly in favour of their having been appended to Charles's thesis by his father. In the *Medical Transactions* of the College of Physicians (London) for 1785 (vol. 3, p. 258) Erasmus Darwin says, "In a pamphlet entitled 'Experiments establishing a criterion between mucaginous and purulent matter, with an account of the retrograde motions of the absorbent vessels,' printed for Cadell, 1780, I subjoined about half a dozen cases of dropsies treated successfully by the decoction of *digitalis;* and endeavoured to distinguish the species of dropsies, in which it would generally succeed. To that account I could now add at least a score of other cases, cured by the same method, of those kinds of dropsy, the seat of which is supposed to be in some part of the *thorax,* and which is attended with *anasarca* of the limbs."

Though Erasmus Darwin was inclined to be unscrupulous, there is scarcely reason to believe that he would claim for himself work that had been done by his son. In the *Zoonomia,* published in 1794 (vol. 1, p. 326), a similar reference is made to his having appended a description of cases treated with foxglove to his son's thesis. Granting then that his statements are accurate, how did it come about that he used and described the effects of digitalis before Withering's celebrated book was published?

Erasmus Darwin has two definite claims to priority in publication: the appendix to his son's thesis which appeared in 1780, and the second paper which was dated Jan. 14, 1785, and read March 16, 1785, bearing the title "An account of the successful use of foxglove, in some dropsies, and in the pulmonary consumption," which as

already mentioned, appeared in the *Medical Transactions*. This paper seems to be little known, and is not referred to by Withering. Well described case reports are given with many more details in each one than had been included in the account of 1780. All the classical symptoms are mentioned, and it was evidently Darwin's practice to push the drug until it produced symptoms of nausea and diarrhoea. Darwin was not the incisive clinical observer that we find in Withering, but his descriptions are not without great merit. His critical faculties were less acute than those of his Birmingham contemporary, and they allowed him to recommend the drug for pulmonary consumption.

Nowhere in any of Darwin's writing on digitalis is Withering's name mentioned, and there is no explanation of how he came to use the drug. The first case in his appendix of 1780 was evidently seen in consultation with Withering, for it is recorded in Withering's book as Case No. IV. Here one finds the probable explanation of Darwin's use of the drug.

It is clear from one case report that Withering was annoyed with Darwin for having published a somewhat garbled and incomplete account of the case which they had seen in consultation. Withering's reference stating that Darwin had trusted to his memory for the details of the case are largely, but not entirely, correct for one finds in Darwin's *Commonplace book* (unpublished, p. 8) the following entry:

> "Miss Hill of Aston near Newport on July 1776 had been indisposed sometime and was then seized with a cough and afterwards a spitting of digested mucus . . . "R Fol. Digitalis."

No mention is made, however, of having seen the case with Withering.

Withering's testimony, however, is clearly correct, that Erasmus Darwin first became acquainted with the action of digitalis on the 25th of July 1776 when seeing Miss Hill in consultation with him. If one applies modern standards of ethics one must conclude that the grandfather of the

celebrated naturalist was somewhat unscrupulous. If priority of publication means anything in these circumstances he indeed has a legitimate claim over Withering. However, one must recognize that it was Withering, and not Darwin, who convinced his medical contemporaries, and it was he who inaugurated the systematic use of the drug; he kept full records of his results, and published after an interval of ten years of careful observation, a full and systematic treatise on its action. Withering's preface is dated "Birmingham, 1st July, 1785." The book itself, presumably appeared sometime in the autumn of that year.

Charles Darwin is mentioned only once in Withering's book, but the passage bears out our inference concerning the likelihood that Erasmus Darwin had informed his son of the action of digitalis. On page 8 Withering states:

"I am informed by my very worthy friend Dr. Duncan, that Dr. Hamilton, who learnt its use from Dr. Hope, has employed it very frequently in the Hospital at Edinburgh. Dr. Duncan also tells me that the late very ingenious and accomplished Mr. Charles Darwin, informed him of its being used by his father and myself, in cases of Hydrothorax, and that he has ever since mentioned it in his lectures, and sometimes employed it in his practice."

Summary.

The evidence which I have just summarized establishes priority of publication concerning the action of digitalis for Erasmus Darwin, but on every other ground, Withering deserves full credit for the discovery. Charles Darwin, the medical student, had been informed of its action by his father and had attempted to account for it on the basis of improvement of lymphatic drainage. But the work, accomplished by the first Charles Darwin is less significant than the abundant evidence of his intellectual ability and precocity, and I have ventured to lay the details of his career before you because of their intrinsic interest and in the hope that the information will serve in a small way to clarify the unsolved problem of the relation of nature to nurture in establishing mental traits and capacities.

COMMITTEE ON PUBLIC HEALTH RELATIONS

REPORT ON VITAMIN D MILK

The City Department of Health requested the opinion of The New York Academy of Medicine relative to the desirability of making energized milk generally available, and the character of Health Department regulations governing the production and sale of such milk.

A subcommittee was appointed to study the various phases of the problem, and the following is the report prepared by the Subcommittee and adopted by the Committee on Public Health Relations.

Reasons for Vitamin D Milk

It has been satisfactorily demonstrated that in order to prevent rickets, children, particularly during the first year of life, require Vitamin D, in addition to that supplied by the usual foodstuffs. Its administration in terms of fish oils is frequently difficult, although these oils are potent and contain easily available D. Administration by means of irradiated ergosterol and other such substitutes for oil is also at times difficult because of taste and gastric intolerance, and is unsatisfactory because of the lessened availability of the contained D. The inclusion of Vitamin D as an integral part of some palatable food, such as milk, removes these objections and assures ease of administration. Moreover, milk is the universal food for infants; carries with it other vitamins; represents in itself the balanced ration; is rich in calcium and phosphorus; and is an important part of the diet during the period when additional D is most needed.

Methods of Producing Vitamin D Milk

Several processes have been developed for concentrating the active vitamin found in cod liver and similar oils. One of the earliest of these, the Zucker process, is now commercially employed to supply additional D units to food, especially to milk.

The commercial concentrate has 1,500 to 1,800 times the Vitamin D content of the Steenbock standard cod liver oil. After being tested by biological assay at the place of production, it is diluted to a standard strength of 150 D (i.e. 150 times the Steenbock standard cod liver oil, or 195 rat units per gram) and sent to the milk distributor. At the milk plant the material (commercially known as Vitex) is again diluted in a can of milk and then distributed into the large supply vats containing measured quantities of raw milk where it is thoroughly mixed and then sent to the pasteurizers. The dilution ratio, standardized concentrate to milk, is about 1:1,200. The total dilution ratio, full strength concentrate to milk, is about 1:12,000. If desirable the standardized concentrate can likewise be made up in a milk dilution so that the latter figure represents the dilution of added foreign substance. Under the plan of distribution at present adopted, samples of the finished product taken in the market are assayed regularly by a University, State Board, or other equally satisfactory laboratory at the expense of the concentrate manufacturer and under the scientific direction of Dr. Zucker and a faculty committee of Columbia University. At the present time about 100 such assays per month are reported from the various laboratories of which about 60 are from milk supplies.

With continuously increasing market demand for preparations of this sort, greatly enhanced by a large demand for a second grade product used in chicken feed, it has been possible to improve the processes of concentration, to elaborate the procedures of biological control, and, by selection, to improve the quality and the uniformity of the first quality product destined for human consumption.

With the discoveries by Steenbock and by Hess of the influence of ultra violet light of certain wave lengths upon ergosterol, and other organic compounds, a second important source of Vitamin D became available and developments in this field have been extensive and rapid. With regard to milk supplies there have been two particular

outcomes of this work, namely, the feeding of cows with irradiated commercial yeast or ergosterol; and more recently, direct irradiation of the milk itself. The latter process has been extensively investigated as to its clinical, electrical, optical and mechanical details and in particular as to chemical changes in the milk itself. It has been found necessary to limit the time of exposure to a few seconds or to make a corresponding decrease in the intensity of the light in order to avoid unfavorable taste-producing reactions upon the milk fats. The carbon arc lamps produce a high concentration of ozone in their immediate neighborhood and special ventilation provisions have to be made to prevent contact of the milk with this substance which likewise reacts on the fats disadvantageously. The antirachitic potency is imparted to the milk rapidly without appreciably affecting Vitamin A and slightly Vitamin C.

Each of these systems of treatment has its specific mechanical and economic advantages. For the small dealer the avoidance of expensive equipment and the ability to mix up from day to day the exact daily requirements of treated milk are controlling items. To the large distributor, there is claimed at the present time for the process of irradiation an actual overall economy despite a rather heavy initial outlay. The situation has not however been sufficiently developed to justify any direct comparison of costs at the present introductory stage.

The concentrate method enjoys the undoubted advantage of flexibility in that dosages of any required quantity can readily be introduced so that milks could, if desired, be put on the market with differing concentrations for specific purposes. The mechanical operations of the two processes at the plant are perhaps about on a par although the actual operations of homogenizing and mixing are quite familiar to milk plant operators. Here again however it is only fair to await developments and satisfactory evidence that proper control mechanisms have been produced.

Physical, Biological and Clinical Tests

There has been some uncertainty and there are certain conflicting opinions upon the question of the rat unit as a criterion of rickets prevention efficiency in the human infant and the facts in this matter must be established before there can be any satisfactory therapeutic use of Vitamin D preparations of various types. This difficulty, however, is a general one not specific to the milk problem and, in view of the flexibility of the concentrate method at least, offers no insuperable difficulty since any specified dosages are readily obtainable. Under the irradiation procedure as now managed it does not seem to be feasible to obtain a much greater concentration than between 50 to 60 rat units per quart.

From the point of view of sanitary production and of administrative details the two systems are about on a par. The concentrate itself is an anhydrous oil which appears to be bacteriologically sterile as would be anticipated from the method of its production. Being added to the raw milk before pasteurization it introduces no serious sanitary problem. The irradiation procedure likewise is from this point of view similar to other milk handling procedures and is likewise safeguarded by subsequent pasteurization. The somewhat technical point, the addition of a foreign substance to the milk, can be practically avoided, if necessary, by diluting the concentrate in pure milk fat or as is now being experimentally tested, by the use of an evaporated milk as a diluent. Any fortification of natural milk with Vitamin D obviously involves certain additions and chemical alterations in the milk and any milk so modified should be properly labelled to comply with basic pure food laws. If such fortified milks are desirable and are to be approved by the board of health, it is rather quibbling to raise the point of an added foreign substance against either of these two processes.

In the milk of yeast-fed cows there may be considerable variation in the number of rat units per quart, which is due to the difference in the amount of irradiated yeast fed

daily. The potency of the milk depends almost entirely upon the amount of irradiated yeast given and one can conclude that if there is any great variation in the potency of milk of cows fed in this manner, there has been some error in the amount of yeast given to the cows.

As important as the content is the degree of utilization of the Vitamin D. By clinical test this is found to be protective in fortified milk when 24 ounces containing 40 units, are given daily. On the other hand, Kramer and Gettleman believe that unit for unit, there is no difference in the action of directly irradiated milk or milk from cows fed irradiated yeast.

Furthermore, Hess and Lewis (*J.A.M.A.*, July 15, 1933) clinically appraised medicinal oils containing 40 units per gram—"3D"—and found the prophylactic base to be 250 units of cod liver oil D. This work seems to indicate that the availability of D in irradiated milk is five times that of the D content in medicinal oil.

One of the most interesting problems in the therapeutics of rickets is the discrepancy between the rat unit content and the clinical efficacy of various anti-rachitic agents. For example, according to Hess and Lewis, 42 rat units (Steenbock) in the form of irradiated milk, bring about a rapid cure of infantile rickets, whereas 80 units of milk from yeast-fed cows, approximately 160 to 240 units of cod liver oil, and 600 to 800 units in the form of viosterol, are necessary to accomplish a similar result. The ratio of effectiveness of irradiated milk, yeast milk, cod liver oil and viosterol, is therefore, from the point of view of rat units, approximately 15 :8 :4 :1. As a result of these experiences it is impossible to predict the clinical potency of a new anti-rachitic agent merely from its rat unitage. The dosage of new agents can be accurately determined only by experiences in the clinic.

On the basis of the already rather extensive evidence it is safe to assert that Vitamin D milks, irrespective of the manner in which they are produced, are capable not only of preventing but also of curing rickets. If all artificially

fed infants were given Vitamin D milk, rickets would become a rare disorder. It should be noted, however, that occasionally infants will develop rickets in spite of receiving a liberal supply of Vitamin D. These cases are often resistant to treatment with even excessively large amounts of Vitamin D, and should they be encountered in infants receiving Vitamin D milk, it should *not* be deduced from such an experience that the fortified milk has proven to be a failure.

There are at present four designations for units and three different strengths and there is need of uniformity in gauging the curative and preventive potency of the Vitamin D milk for clinical use as well as for health administration purposes.

The assay of the D content of such fortified milks has been time-consuming and expensive. When stated in terms of rat units, the D value must be translated into clinical units and the values of the various forms of D carrying material can not be considered as interchangeable.

Biological assay of energized milk consumes three weeks and provides information too late for practical value.

The most critical detail, however, is the control of the character and intensity of the illumination to secure a uniform and predetermined concentration of the vitamin in the milk. Some very excellent apparatus has been developed for measuring and recording the energy output of the radiating lamp in a certain limited range of the spectrum. It may safely be assumed that these instruments will produce accurate records. The following further assumptions are necessary, however, to justify the acceptance by the administrative officials of any such record as a criterion of Vitamin D productions:

(a) The effectiveness of the various wave lengths of ultra violet light in their ability to produce Vitamin D is paralleled by their respective powers to excite the photoelectric response in the measuring apparatus.

(b) The formation of Vitamin D in milk is a function only of the incident radiation and not of such other physical conditions as temperatures of the milk, chemical composition, etc.

(c) The mechanical details of the operation which determine the time of exposure of the milk to the rays, the thickness of the exposed film, etc., have been so perfected that these important factors may be safely considered to be held constant.

Item (a) has been established by controlled experiment with a reasonable degree of approximation for the limited conditions of the tests. The other items have received only secondary mention.

This indirect test may be capable of complete and satisfactory standardization and would, if so standardized, be of the greatest assistance in the administrative control of the product of Vitamin D milk. Its acceptance for this purpose however must await the most thoroughgoing study of its true significance and during this introductory stage any new installation should be subjected to an extensive over-all calibration of the physical measuring device against the actual anti-rachitic potency of the milk.

Vitamin D Milk for General Consumption

In regard to the question of the possibility of toxic effects resulting from Vitamin D milk, it may be of interest that no one has ever observed any untoward symptoms or hypercalcemia resulting from its administration. It seems that the low titre of rat units in energized milk would preclude such a possibility. Furthermore, feeding rats 10,000 times a therapeutic dose of Vitamin D milk for a period of months did not bring about any deleterious effects, or any abnormal histological changes in the tissues. On the other hand, the need of additional D for well adults is not satisfactorily proven. There is evidence indicating the advantage of additional D in conditions associated with low calcium, in dental caries, during parturition and lactation, perhaps in chronic bone disease and possibly in tuberculosis.

The advisability, therefore, of universal or general energizing of milk does not seem apparent.

Administrative Problem

Assuming that the need for Vitamin D milk has been established, the question then arises as to the responsibility, if any, of official governmental agencies for the regulation and control of the production, handling and sale. This is a question which the committee has considered only because it has been advised that the health departments of the state and the city of New York would welcome an expression of its views.

Apparently neither the State Public Health Council nor the New York City Board of Health has yet undertaken to establish detailed requirements in their respective codes. The State Sanitary Code contains the brief definition that "The term 'Vitamin D milk' means milk in which the Vitamin D content has been artificially increased" and the general provision that it must be made from milk meeting the applicable requirements of the code for milk sold under grade designation. The committee is informed that the question of the need for additional and more specific requirements has been considered by the State Department of Health and the Public Health Council in the recent past and it has been felt that it would be unwise to establish more specific or detailed requirements while the production of Vitamin D milk is still in an experimental stage and until the various scientific and administrative problems involved are better understood.

The State Department has taken the tentative position that it would neither endorse the product nor interfere with its sale so long as it conformed to the above mentioned general requirements. It has felt that this "neutral" position was justified in view of the apparently well founded claims as to the need among children for the product and inasmuch as the possibility of harm resulting from its sale was very remote, providing the milk used was of safe sanitary quality.

It would seem that the principal immediate administrative problem, from the standpoint of protecting the public, is that of assuring that Vitamin D milk sold actually contains the amount of the vitamin which it is represented to contain. It would seem that the health departments, having jurisdiction in matters relating to the sanitary quality and healthfulness of milk, would be the logical agencies to assume such responsibility, so far as it is practicable. From the above discussion it is apparent that the problem is not a simple one. The question of the relative merits of the three available units of measurement is still not completely settled. There are still differences of opinion as to the effectiveness per "unit"—depending on the unit selected—of the vitamin as added by different processes and pending further clinical experimentation it does not seem desirable as yet to form definite conclusions as to what the minimum acceptable standard amount of the vitamin per quart of milk should be. The laboratory procedures required to determine the amount of the vitamin in a specific quantity of milk are involved and expensive and thus far have been undertaken in only a few laboratories, including those maintained and operated for commercial purposes. In view of the expense involved it would not seem to be feasible, under present conditions, for health departments to attempt to set up and finance independent official laboratory service to carry on this work, especially considering the fact that the sale of Vitamin D milk is still limited and that the product is in a sense proprietary.

Involved in the public health aspects of the matter is the question as to what, if any, hazard is involved in the addition of a foreign substance to milk, as is necessary in one of the recognized procedures for increasing the Vitamin D content. While it may be "splitting hairs," the general feeling seems to be that the indirect addition of Vitamin D to milk through irradiation and through the feeding of irradiated yeast to cattle need not be considered the addition of a foreign substance in the commonly accepted sense but that this can not properly be held to apply to the addition of a definite physical substance, as in the case of the

Zucker cod liver oil concentrate. The committee feels safe in venturing the opinion that, considering the fact that this concentrate when it leaves the manufacturer is practically a sterile product, the fact that the amount added to milk is small and the further fact that the procedure involved in adding the concentrate to the milk by the distributor is one not requiring contact with human hands and offering little opportunity for contamination, the hazard, if any, would be so slight as to be negligible, providing the milk was pasteurized after the addition of the concentrate.

Looking at the matter purely from the standpoint of medicine and health, the committee at the moment is unable to see any valid objection to permitting the addition of Vitamin D to milk by any of the recognized methods, under properly controlled conditions.

In view of the fact that the production of Vitamin D milk is still experimental, that existing methods may be changed or improved and, conceivably, new methods may be evolved; that the relative values of units of measurement and the basis for establishing minimum standards for Vitamin D content are still unsettled; and in view of the limited availability of laboratory service for the purpose of making assays, the committee is inclined to feel that the official health agencies in the State and in the City of New York would be acting wisely if they continued, for the present, to defer the enactment of detailed and specific requirements beyond those necessary to assure that the ultimate product be of a safe sanitary quality.

The committee therefore is of the opinion that Vitamin D milk, produced by any one of the three methods, should be allowed to be sold, the containers to carry a label to the effect that it is Vitamin D milk, indicating also the process used. As to whether or not health regulations should require that the label specify that the milk contains a certain specified minimum number of protective units, say 50 per quart, is a matter with regard to which there is still a considerable amount of difference of opinion.

Theoretically, it would be desirable for the producers to state on each bottle the number of units of Vitamin D present in the milk, but in view of the fact that health departments have no laboratory facilities for assaying milk, it is questionable whether this requirement would be practicable. It might perhaps, for the time being at least, be more desirable that the label merely state the source of Vitamin D in each instance, the health department to decide what it considers a normal protective dose and in its license provisions demand proof from time to time that the milk produced under the license contains the stated dosage.

From the evidence now available, the Committee is of the opinion that such requirement will be satisfactorily fulfilled by

1. Directly irradiated milk containing 56 rat units per quart.

2. Concentrate milk and yeast-fed milk containing 100 rat units per quart.

This report was prepared by a special subcommittee consisting of:

HERBERT B. WILCOX, *Chairman*

PAUL BROOKS (Albany)

J. M. LEWIS

EDGAR MAYER

EARLE B. PHELPS

E. H. L. CORWIN, *Secretary*

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MARIE SKLODOWSKA CURIE

1867-1934

Madame Marie Sklodowska Curie died at Sallanches, France, on July 4th, 1934, aged 66 years. For the last several years she had been in failing health, and her death was due to pernicious anemia, in all probability resulting from long exposure to radium. Madame Curie was born in Warsaw, Poland, July 7th, 1867.

She was married to Prof. Pierre Curie in Paris in 1895. Following the discovery by Becquerel of radioactivity in uranium they began their efforts to identify the radioactive element, and in 1898 they succeeded in isolating radium metal from pitchblende. In later years most of her researches were directed to the study of the remarkable physical properties of polonium, a decomposition product of radium, which proved to be of great value to the science of physics. After the death of her husband, in 1906, she was appointed to succeed him as professor of physics in the University of Paris. In 1911 she received the Nobel prize, and later many other honors and prizes were awarded to her. The most significant was the establishment, by the University of Paris, of the Radium Institute, in which she was appointed head of the research department, a position which she occupied actively until her death.

In 1921 she visited America to receive the gift of a gram of radium secured by American admirers, chiefly women, and presented by President Harding. At this time she visited many physical laboratories and several cancer hospitals and attended many complimentary functions. She took a keen and highly intelligent interest in the application of radium to the treatment of cancer. She returned to America in 1929 to receive a gift of $50,000 raised by many friends and presented by President Hoover at the National Academy of Science in Washington. In 1930 she was elected an Honorary Fellow of The New York Academy of Medicine.

Madame Curie remained throughout her life a woman of simple tastes and modest requirements. She received her numerous honors with graceful reserve, but full appreciation. She was extremely direct and simple in her approach to every problem. She was always ready to discuss freely any subject in which she felt herself competent, but was chary of speculations and predictions. In her death passes one of the most cultivated feminine minds and distinguished investigators in the history of science.

JAMES EWING.

DEATH OF FELLOW OF THE ACADEMY

LEALE, MEDWIN, B.A., M.D., 555 Park Avenue, New York City; graduated in medicine from the College of Physicians and Surgeons, New York City, in 1896; elected a Fellow of the Academy December 3, 1908; died, June 30, 1934. Dr. Leale was a Fellow of the American Medical Association, a member of the County and State Medical Societies, The Pathological Society, the Roosevelt Hospital Alumni Association and the Alumni Association of St. John's Guild. He was Consulting Physician to St. John's Hospital in Brooklyn, Nassau Hospital in Mineola, and North Country Community Hospital in Glen Cove.